Mechanisms by Which Cancer Chemotherapeutic Drugs Induce Emesis

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Because the area postrema seems essential for chemotherapy-induced vomiting, both circulating and/or neurally mediated stimuli in this area could trigger the emetic response. In our laboratories results of cross-circulation and direct intracerebroventricular infusion experiments in dogs do not support a role for circulating substances. The large increases in serum vasopressin induced by cisplatin were not blocked by inhibitors of the angiotensin-converting enzyme. In the ferret inhibition of serotonin synthesis with p-chloro-phenylalanine, administration of selective antagonists of 5-hydroxytryptamine$_3$ (5-HT$_3$) receptors, or visceral deafferentation inhibited the emetic response evoked by cisplatin or high-dose cyclophosphamide. The results suggest that serotonin plays an important role and that peripheral neural mechanisms are involved in the emetic response. The strong antiemetic efficacy of selective 5-HT$_3$ antagonists also has been confirmed in humans. In cancer patients high-dose cisplatin increased the plasma and urinary levels of 5-hydroxy-indoleacetic acid (5-HIAA), but did not affect platelet and free plasma serotonin. The changes in 5-HIAA levels paralleled the onset and development of vomiting. No evidence of serotonin depletion has been obtained after high-dose cisplatin. Dacarbazine, another strongly emetogenic agent, increased urinary 5-HIAA; however, only small increases in 5-HIAA were produced with low-dose cisplatin or cyclophosphamide-containing regimens. Thus, emetogenicity appears to be directly related to the ability of the cytotoxic agent to release serotonin. In humans, antiemetics such as ondansetron, metoclopramide, and dexamethasone did not effect high-dose cisplatin-induced increases in serotonin metabolism. Therefore, these antiemetics seem not to affect the amount of serotonin released. The mechanism by which chemotherapeutic drugs induce serotonin release is unknown; however, release may occur by direct cytotoxicity on the gastrointestinal mucosa, including the enterochromaffin cells. Delayed emesis appears to be mediated by 5-HT$_3$–independent mechanisms. It is proposed that emesis that develops despite high-dose ondansetron (residual emesis) should be considered delayed emesis. Residual and delayed episodes of emesis have similar time courses, are characterized by very mild emetic episodes and poor response to 5-HT$_3$ antagonists, and are not associated with increases in serotonin metabolism.

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CHEMOTHERAPY-INDUCED NAUSEA AND EMESIS: STATEMENT OF THE PROBLEM

NAUSEA and vomiting are common and disabling side effects of cancer chemotherapeutic drugs. They also can be induced by high-dose radiation, particularly when applied to the abdomen and pelvis.[1-3] Typically, nausea and emesis due to chemotherapy and radiation therapy develop after a relatively fixed latency time following each course of treatment. In the absence of effective antiemetic protection, chemotherapy regimens based on high-dose cisplatin induce vomiting in almost all patients. Vomiting starts 2 to 3 hours after chemotherapy; it lasts approximately 8 hours, and an average of 10 to 12 intense emetic episodes may develop during this period.[4-6] For cyclophosphamide-based chemotherapies, the time to vomiting averages 10 hours. The vomiting is of moderate intensity and may last 12 to 24 hours.[6-8] After this initial, more intense period of vomiting, nearly 70% of patients treated with high-dose cisplatin may develop a milder form of nausea and vomiting, which may last 3 to 5 days and is known as delayed emesis.[9,10] Delayed emesis is not observed with all chemotherapeutic drugs.[9]

In the last 5 years, a great effort has been devoted to the understanding of the mechanisms of the nausea and vomiting associated with chemotherapeutic drugs and irradiation and to the development of new and more effective forms of treatment. This essay will focus on emesis induced by chemotherapeutic drugs. When appropriate, available mechanistic information about emesis associated with irradiation is presented. Emphasis will be placed on critically analyzing the most relevant data on the role of serotonin in chemotherapy-induced emesis. To allow a better comprehension of the subject, a brief review on how the thought process evolved in this field is presented.

ROLE OF THE CHEMORECEPTOR TRIGGER ZONE

Vomiting induced by many endogenous compounds and xenobiotics involves the chemoreceptor trigger zone (CTZ), which is located in the vicinity of the area postrema, a richly vascularized circumventricular organ located on the caudal margins of the fourth ventricle. The CTZ is anatomically and functionally distinct from the vomiting center. The latter is located in the dorsal portion of the lateral reticular formation and mediates the coordinated reflexes associated with the act of vomiting.[11-14] Ablation of the area postrema has been shown to prevent vomiting induced by irradiation or alkylating agents in the dog.[15] In the cat, however, surgical ablation of the area postrema was ineffective in blocking irradiation or nitrogen mustard-induced emesis.[16] These and other pieces of information indicate the existence of species differences in the pathways and mechanisms mediating chemotherapy- and irradiation-induced emesis. It should be emphasized that prevention of vomiting by ablation of the area postrema does not indicate that the mechanism is humoral, since this region receives important neural afferents. Also, it does not indicate that the emetic stimulus acts on the area postrema, since it may well be that the area postrema is on the pathway of the emetic reflex.

EXPERIMENTAL MODELS TO EXPLAIN CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Several models have been proposed to explain the emetic response associated with chemotherapy and radiation therapy.[16-18] In these models, for reasons of simplicity, it has been assumed that radiation therapy and chemotherapeutic drugs induce emesis by a similar mechanism. Nevertheless, it is possible that different mechanisms may apply, even between chemotherapeutic agents.

Model of the Direct Action on the Vomiting Centers

The direct interaction model is a simple one and proposes that the anticancer drugs and/or their metabolites would act directly on receptors located in the CTZ (area postrema) and/or vomiting centers. However, the following factors argue against this model: (1) it is unlikely that the CTZ would have a large number of receptors sensitive to each of the chemotherapeutic drugs, (2) the long latency time to the onset of emesis is not consistent with a direct action of the emetic drugs on the CTZ, (3) irradiation of the head produces less vomiting than irradiation to the abdomen, and (4) vagotomy and sympathectomy abolish cisplatin-induced emesis in the ferret, indicating an indirect action of chemotherapy.[19]

Humoral Model

The humoral model assumes that endogenous factors are formed after radiation or chemotherapy and that these factors would stimulate the CTZ and/or the vomiting centers via the circulation. The time to onset of emesis would reflect the time for synthesis and/or release of the humoral factors. Since the primary receptor for the anticancer drugs is DNA, it is possible that the damaged cells could release factors that would be sensed in the central nervous system (CNS). Drugs that damage DNA or inhibit DNA replication are more emetogenic than agents that do not directly affect DNA. This model predicts that the blood factor could be transferred from a donor to a recipient animal.

Several experiments have been conducted in dogs to test the humoral model. In chronically implanted dogs and cats, the intracerebroventricular administration of plasma, plasma ultrafiltrates, and concentrated plasma ultrafiltrates derived from donor animals that were vomiting following cisplatin failed to induce retching or vomiting in the recipient animals.[16] In addition, in blood type-matched dogs administration of heparinized whole blood directly from a vomiting dog via a catheter placed in the vertebral artery did not induce vomiting in the recipient dog. Finally, cross-circulation experiments through the femoral arteries and veins, performed in blood type-matched dogs (one recipient and one donor), revealed that the emetic stimulus induced by the administration of cisplatin into the donor dog could not be transferred to the recipient dog.[16] These findings argue against the humoral model, ie, the existence of circulating substances released by cisplatin that could stimulate the vomiting sensing areas to induce vomiting.

Model of the Neural Afferents

In its simplest form, the model of the neural afferents proposes that chemotherapeutic drugs

and/or irradiation activate nerve afferents, increasing the neural input to the CTZ and/or the vomiting center. This model has been tested by surgical destruction of the proposed afferent fibers. Neural inputs from both the vagus and sympathetic fibers via the spinal cord play important roles in the mediation of vomiting induced by chemotherapeutic drugs. Sections of both vagal and sympathetic inputs prevented cisplatin- and x-radiation–induced emesis in the ferret, and radiation- and nitrogen mustard-induced emesis in the cat. In the monkey, supradiaphragmatic vagotomy prevented vomiting from total body irradiation.[11-13,18,19]

Although these experiments support the neural model, they do not indicate the mechanism by which the fibers are stimulated or the nature of the stimulus. As for the direct interaction model, it is unlikely that the afferent fibers would have receptors for each of the chemotherapeutic agents and for irradiation. It is most likely that a common substance or mechanism would be produced or released by anticancer drugs and irradiation and that this substance(s) would trigger the vomiting reflex acting on nerve fibers. Therefore, the humoral model, which assumes the presence of a circulating substance common to most chemotherapeutic drugs and to irradiation, may be wrong only because the common factor does not circulate, but rather acts locally to activate neural afferent fibers. The common emetic stimulus may be formed and/or released on the abdominal viscerae. This is supported by the observations that irradiation to the abdomen produces the most nausea and vomiting and that visceral denervation prevents emesis induced by irradiation, cisplatin, and nitrogen mustards in experimental animals.[18]

The Common Factor

Several substances have been proposed to mediate chemotherapy- and radiation therapy-induced emesis. Dopamine, prostaglandins, several peptides, and, more recently, serotonin have been considered as candidates. Studies by Harding et al[15] and Carpenter et al[20] revealed that systemic and/or intracerebroventricular administration of neurotensin, angiotensin II, or vasopressin induces emesis in animal models.[15,20] Of these substances vasopressin seems the most likely candidate. For example, in both animals and humans, very large increases in plasma vasopressin levels have been observed following different emetic stimuli.[21-23] In the dog, cisplatin induces 30-fold increases in plasma vasopressin levels without significantly affecting the plasma levels of angiotensin II.[24] The magnitude of increase produced by cisplatin is far greater than that evoked by osmotic mechanisms and occurs without changes in serum osmolality. Since vasopressin has been shown to induce vomiting when administered intracisternally or intracerebroventricularly, the high levels of vasopressin could mediate at least part of the emetic response produced by chemotherapeutic drugs.

The mechanism of the increases in vasopressin release have been partially elucidated. Studies by our group indicated that cisplatin-induced increases in arginine vasopressin (AVP) were not mediated by parallel increases of angiotensin II, a well-known powerful stimulant of vasopressin release. In fact, inhibition of the angiotensin-converting enzyme with enalapril failed to prevent cisplatin-induced vomiting and increases in plasma AVP.[24] Furthermore, Hawthorn et al demonstrated that visceral denervation prevented cisplatin-induced emesis, as well as cisplatin-induced increases in AVP levels, and that visceral, vagal afferent stimulation induces AVP release.[25] These studies indicate that in the ferret, and perhaps in the dog, the increases in AVP levels, as well as the emetic response, are neurally mediated. The fact that other emetic stimuli, such as apomorphine, also induce increases in plasma AVP suggests that AVP may be a compensatory response associated with nausea and emesis rather than the cause of these effects. As we have proposed, the marked increase in AVP secretion is a desirable response in anticipation of fluid losses leading to water conservation in animals and humans experiencing nausea and emesis.[24]

THE SEROTONIN HYPOTHESIS: SEROTONIN, THE COMMON FACTOR

Recent observations in animals and humans revealed that selective antagonists of serotonin type-3 receptors (5-hydroxytryptamine$_3$ [5-HT$_3$] antagonists) are very effective against nausea and vomiting associated with chemotherapy and radiation therapy.[8,10,18,26,27] These findings renewed interest in the role of serotonin as the common local factor. The following additional evidence

further supports the serotonin hypothesis: (1) cisplatin increases the turnover of ileal serotonin in the ferret,[28] (2) depletion of tissue serotonin with p-chloro-phenylalanine inhibited cisplatin-induced emesis in the ferret,[29] (3) administration of cisplatin in the isolated mesenteric beds induces the release of serotonin in guinea pigs,[30] (4) the presence of 5-HT_3 receptors in vagal afferent fibers, which when activated by serotonin increase the firing rate of these fibers,[18] and (5) increases in serotonin release and metabolism occurring in close temporal relationship with the development of nausea and emesis have been reported following cisplatin-based chemotherapies in cancer patients.[6,10,31]

Testing the Serotonin Hypothesis in Humans: Changes in Serotonin Levels and in Serotonin Metabolism Induced by Cancer Chemotherapeutic Drugs

If serotonin mediates nausea and emesis associated with chemotherapeutic drugs, evidence of increases in serotonin release could be obtained by measurement of serotonin and serotonin metabolites in biologic fluids.

Changes in 5-hydroxy-indoleacetic acid (5-HIAA) induced by cisplatin. In the first study we measured the urinary excretion of 5-hydroxy-indoleacetic acid (5-HIAA) in 24 cancer patients and the plasma levels of 5-HIAA in 16 patients. These measurements were performed prior to, during, and after the first course of chemotherapy with ≥ 50 mg/m^2 of cisplatin (average dose, 76 ± 6 mg/m^2). Half of the patients received ondansetron and the other half received placebo (rescue antiemetics). We observed an increase in the plasma levels and in the urinary excretion of 5-HIAA, both of which occurred in parallel with the onset and development of emesis (Tables 1 and 2).[31] Nearly 1.5 mg of 5-HIAA above baseline was excreted from 2 to 8 hours following cisplatin infusion.[10,31] At 3 to 5 hours after cisplatin administration, 5-HIAA concentrations were double those at baseline. Subsequently, the plasma levels of 5-HIAA declined, returning to baseline 9 hours after cisplatin (Table 1).

To determine the possible contribution of increase in urine flow induced by fluid load and mannitol, a study was conducted in six healthy subjects who received hydration and mannitol therapy similar to that given to the cancer patients. The urinary excretion of 5-HIAA did not increase in healthy volunteers throughout the 24-hour period of observation, indicating that the changes in serotonin metabolism observed in the cancer patients were most likely due to the chemotherapy. Interestingly, when compared with the daily samples, a reduction in the urinary excretion of 5-HIAA was observed in the late evening-nocturnal urine sample (Table 1).[31]

Changes in plasma and platelet serotonin levels induced by cisplatin. In 16 cancer patients receiving chemotherapies containing high-dose cisplatin (75 ± 5 mg/m^2), we measured the concentrations of serotonin in platelet-free plasma and the platelet serotonin content before, during, and after their first course of chemotherapy with ≥ 50 mg/m^2 of cisplatin. Ninety-eight percent of blood serotonin was present in platelets, and the total amount of serotonin in blood was estimated to be between 0.8 mg and 1.4 mg. No changes in the content of serotonin per platelet, the number of platelets, or the concentration of serotonin per milliliter of plasma were observed over the 10-hour period that followed the infusion of high-dose cisplatin.[31] Free circulating serotonin levels (platelet-free plasma) showed a small increase 3 to 7 hours after cisplatin, yet the increase was not significant (Table 2). In a recent report by Barnes et al,[32] marked increases in platelet-free plasma serotonin levels were demonstrated in four out of 10 patients receiving treatment with cisplatin, etoposide, and bleomycin for metastatic germ cell

Table 1. Changes in the Urinary Excretion of 5-Hydroxy-indoleacetic Acid Induced by Chemotherapy

	Time (hr)				
Chemotherapy	0-2	2-4	4-6	6-8	8-24

Note: Urinary 5-HIAA excretion was measured in 2-hour samples. Baseline sample (−2 to 0 hour) started 2 hours before initiation of chemotherapy. Time 0 is the time at which the infusion of the main chemotherapeutic agent was begun. The infusion lasted 1 hour. Other chemotherapeutic drugs were administered thereafter. Controls were healthy subjects who received hydration and mannitol and did not receive chemotherapy. The negative symbols indicate percentage of decrease from baseline. Other values indicate percentage of increase above baseline.

Abbreviation: NA; not available.

* Significantly different from baseline (at least $P < .05$).

Table 2. Changes in the Plasma Levels of Serotonin and of 5-Hydroxy-indoleacetic Acid Induced by Chemotherapy

Variable	Percentage Increase Above Baseline at Indicated Time (hr)		
	3	5	9
		47 ± 10	47 ± 10
		105 ± 19	80 ± 19

Note: Plasma 5-HT and 5-HIAA were measured before and after initiation of high-dose cisplatin chemotherapy. Time 0 (baseline) is the time at which the infusion of cisplatin was begun. The infusion lasted 1 hour. Other chemotherapeutic drugs were administered thereafter. 5-HIAA values at 3, 5, and 7 hours were significantly different from baseline (at least $P < .05$).

tumor of the testis. The reasons for the differences between the studies are unknown; however, there are several possible factors: (1) the doses of cisplatin were probably lower in the latter study compared with the former study, (2) in the study of Barnes et al, in three of the four patients who experienced changes in plasma serotonin the increases were observed only at a single time point, and (3) differences in the methodology used for the preparation of the plasma and the use of an extraction step prior to the high-pressure liquid chromatography may explain the higher basal levels of serotonin observed in our study.[31]

Effects of other chemotherapeutic drugs on serotonin metabolism. We next investigated whether another strongly emetogenic agent, dacarbazine, induced increases in the release and metabolism of serotonin.[31] Dacarbazine-based (283 ± 22 mg/m^2) chemotherapy regimens (associated with either doxorubicin, iphosphamide, or cyclophosphamide) induced a marked and early increase in the urinary excretion of 5-HIAA, which peaked 3 hours after initiation of the dacarbazine infusion (Table 1). The magnitude of the increase was comparable to that observed with high-dose cisplatin and paralleled the time course of the vomiting in those patients; in fact, the time to onset of emesis after dacarbazine was 2.5 hours. The 5-HIAA levels returned to baseline 10 hours after cisplatin. These results provide strong additional support for the serotonin hypothesis. In fact, most experimental data in support of this hypothesis had been obtained with high-dose cisplatin. The effects of dacarbazine indicate that structurally different chemotherapeutic drugs act through a common mechanism, ie, the release of serotonin from the gastrointestinal tract.

Subsequently, we investigated the possible existence of a relationship between the amount of serotonin released (urinary 5-HIAA) and the intensity of vomiting. According to the serotonin hypothesis, lesser emetogenic regimens should produce smaller increases in serotonin release and thus in the excretion of 5-HIAA. This was investigated by comparing the effects of high-dose cisplatin on serotonin metabolism with those of low-dose cisplatin and cyclophosphamide-based chemotherapies (Table 1).

A parallel study was conducted in 17 chemotherapy-naive cancer patients receiving non-cisplatin, cyclophosphamide-based chemotherapies (≥500 mg/m^2). The urinary excretion of 5-HIAA was measured at 2-hour intervals. Only a small increase (30% above baseline) in the urinary excretion of 5-HIAA was observed during the first 8 hours following chemotherapy, a time interval at which there is no vomiting (Table 1). However, the 5-HIAA/creatinine level encountered in the urine sample collected from 8 to 24 hours post-cyclophosphamide failed to decline, whereas in the control group of healthy volunteers 5-HIAA decreased by 50% (from 5.8 ± 1 ng to 2.4 ± 0.3 ng of 5-HIAA/μg of creatinine) in the evening-nocturnal urine sample. Therefore, compared with the control group cyclophosphamide produced an increase in 5-HIAA excretion, but this increase was smaller and more delayed than that observed with high-dose cisplatin (Table 1). These biochemical observations correlate with the characteristic less-intense and more-delayed emetic response produced by cyclophosphamide-based chemotherapies compared with high-dose cisplatin.[4,5,7,8,10]

A trial conducted in chemotherapy-naive patients revealed smaller increases in the urinary excretion of 5-HIAA in the low-dose cisplatin group (31 ± 3 mg/m^2) compared with the high-dose cisplatin group. For low-dose cisplatin, increases above the baseline were observed only in the urine samples collected from 6 to 8 hours and from 8 to 10 hours following chemotherapy.[31] Only half of the low-dose cisplatin-treated patients showed increases in 5-HIAA, whereas 5-HIAA increased in all patients in the high-dose group. Therefore, it was observed that high-dose cisplatin produces greater increases in 5-HIAA excretion and more intense emesis (despite

antiemetic treatment) than low-dose cisplatin (Table 1).

In summary, despite inducing moderate emesis, only a small increase in 5-HT metabolism was observed with cyclophosphamide and low-dose cisplatin. However, emesis is blocked by 5-HT_3 antagonists, suggesting that emesis is mediated by serotonin acting on 5-HT_3 receptors. With low-dose cisplatin there is less 5-HT released, milder emesis, and better antiemetic control (see below). With high-dose cisplatin and dacarbazine there is more 5-HT released, stronger emesis, and poorer antiemetic control. It appears that the dose of cisplatin determines the amount of serotonin released and thus the magnitude of the emetic response. Consequently, emetogenicity appears to be related directly to the ability to release 5-HT: stronger emetogenic regimens (high-dose cisplatin or dacarbazine) release larger amounts than moderately emetogenic treatments (low-dose cisplatin or cyclophosphamide).

Effects of antiemetics on serotonin metabolism. The effects of antiemetics on high-dose cisplatin-induced increases in serotonin metabolism have been evaluated.[6,10] In one study, ondansetron (0.15 mg/kg every 4 hours, three doses), a selective antagonist of 5-HT_3 receptors, was compared with placebo (no preventative antiemetic treatment). Comparable increases in the amount of 5-HIAA released (in milligrams) and in the percentage of increase above baseline for the 5-HIAA excretion were observed in the placebo- and ondansetron-treated patients. In a more recent investigation, the effects of metoclopramide (2 mg/kg, every 4 hours × 2) were compared with those of dexamethasone (20 mg, every 4 hours × 2). No significant differences in 5-HIAA excretion were found between the treatment groups. In addition, comparable increases in 5-HIAA excretion induced by high-dose cisplatin were encountered for placebo-, ondansetron-, metoclopramide-, and dexamethasone-treated patients. These results in cancer patients receiving their first course of chemotherapy with high-dose cisplatin suggest that the formation and excretion of 5-HIAA is not blocked by the antiemetics described above. If 5-HIAA is a marker of the released serotonin that acts on 5-HT_3 receptors to trigger nausea and vomiting, the results suggest that ondansetron and metoclopramide, selective and nonselective 5-HT_3 receptor antagonists, respectively, do not act by interfering with the release of serotonin. More importantly, these findings indicate that the increases in serotonin release are not due to the act of vomiting, but to the effects of the chemotherapeutic drug.

However, other mechanisms should not be disregarded. For example, in the vascularly perfused small intestine of the guinea pig, selective antagonists of 5-HT_3 receptors inhibited cisplatin-induced release of serotonin and 5-HIAA.[30] In this preparation, cisplatin induces a short-lasting, neurally evoked release of serotonin from enterochromaffin cells. Although there is no evidence that this mechanism operates in cancer patients receiving cisplatin-based chemotherapy, such a possibility should not be overlooked. Unfortunately, ondansetron, as well as metoclopramide, failed to prevent cisplatin-induced increases in serotonin metabolism in patients.[6,10] It is possible that the effect of cisplatin described by Schworer et al[30] could account for the small part of the total release of serotonin evoked by the cytotoxic agents.

Selective 5-HT_3 antagonists also may have a central site of action. For example, the central administration of 5-HT_3 antagonists prevents vomiting induced by cisplatin.[33] This is relevant, since the largest concentration of 5-HT_3 receptors in the CNS is in the nucleus tractus solitarius-area postrema regions, where the CTZ is located and where most vagal afferents enter the brain.[34]

Site of Release of Serotonin

In humans, nearly 80% (6 to 9 mg) of the serotonin body content is in the gastrointestinal tract, 95% of which is in enterochromaffin cells. The rest of the body serotonin is divided between platelets (11% or 1.5 to 2 mg) and other tissues (1 mg), including the CNS.[35] The increase in urinary 5-HIAA induced by high-dose cisplatin averaged 1.5 mg. Since there were no significant changes in the pool of platelet serotonin, the increase in 5-HIAA should originate from the enterochromaffin cells of the gastrointestinal tract. This proposal is further supported by (1) experiments indicating that in normal subjects, as well as in laboratory animals, 5-HIAA is a marker of gastrointestinal serotonin content and turnover,[36-40] (2) cisplatin increases the turnover of ileal serotonin in the ferret,[28] (3) in guinea pigs, administration of cisplatin in the isolated mes-

enteric beds induces the release of serotonin,[30] and (4) a correlation has been demonstrated between intestinal mucosal damage and severity of emesis in ferrets.[28]

Since platelet serotonin failed to rise after cisplatin, the serotonin released from enterochromaffin cells should be converted to 5-HIAA within the gut wall and/or during its passage through the liver (a first-pass extraction has been demonstrated for serotonin). The free serotonin within the gut wall, rather than the circulating serotonin, may be the form that plays an active role in chemotherapy-induced emesis. This explains the lack of intense vomiting in patients with carcinoid tumors (neoplasms of enterochromaffin cells) despite the presence of very elevated levels of circulating serotonin.[41]

According to the current model, to induce vomiting, serotonin should be released within the intestinal wall (from enterochromaffin cells) and activate the 5-HT_3 receptors located on visceral afferent fibers (vagal and sympathetic). Activation of these receptors would increase afferent nerve firing to the vomiting-controlling centers of the brain.

Mechanisms of Serotonin Release by Chemotherapeutic Drugs

The mechanism(s) by which chemotherapeutic drugs induce the release of gastrointestinal serotonin is unknown. However, there are several major possibilities: (1) the damage of the gastrointestinal mucosa induced by cytotoxic agents induces the release of serotonin, (2) chemotherapeutic drugs stimulate neural fibers, increasing the release of acetylcholine, which acts on receptors located on enterochromaffin cells and induces the release of serotonin, and (3) a combination of both possibilities.

Damage to the gut mucosa. The presence of receptors in enterochromaffin cells for each of the cytotoxic agents is unlikely. Rather, a mechanism related to their cytotoxicity is more likely. Cells of the gut mucosa have a rapid division rate and are thus very sensitive to chemotherapeutic drugs. Rapid cell killing may release substances from dying cells that could induce the release of serotonin, although it is also possible that the serotonin-containing cells are among those severely damaged by the cytotoxic agents. In support of this model is the observation that the stable, long-acting analog of somatostatin, octreotide, failed to prevent emesis as well as the increases in urinary 5-HIAA induced by cisplatin in cancer patients.[31] Yet, this agent is very effective in inhibiting serotonin release from carcinoid tumors.[41] In addition, studies in the ferret revealed that cisplatin produces severe mucosal damage of the ileum and jejunum and that the extent of the damage is related to the severity of the emesis.[28]

Neurally mediated release. Recent studies in vascularly perfused isolated segments of the guinea pig small intestine revealed that infusion of cisplatin induces an increase in the venous outflow of serotonin and of 5-HIAA.[33] Because most of the intestinal serotonin is located in enterochromaffin cells, the increase in serotonin outflow most likely represents release from these cells. This cisplatin-evoked release of serotonin was inhibited by any of the following treatments: scopolamine, hexamethonium, antagonists of 5-HT_3 receptors, tetrodotoxin, or absence of extracellular calcium. The results suggest that cisplatin acts by activation of neural pathways that lead to the release of acetylcholine, which, acting on muscarinic receptors, would stimulate serotonin release from enterochromaffin cells. However, it is unlikely that this effect would be of clinical significance because (1) cisplatin-induced serotonin release was only observed if an unphysiologic buffer (HEPES buffer) was used and could not be elicited when the mesenteric bed was perfused with phosphate- or bicarbonate-containing physiologic solutions; (2) the guinea pig does not vomit when treated with cisplatin; (3) cisplatin-induced serotonin release occurred immediately after initiation of the cisplatin infusion, peaked at 15 minutes, and returned to baseline values within 20 minutes, despite continuous infusion of the cytotoxic agent (this time course does not agree with the typical latency time for the onset of emesis after cisplatin, with the duration of the period of emesis, and with the time course of the increases in 5-HIAA observed in patients); and (4) the increase in release was elicited only by 3 μmol/L cisplatin (lower concentrations were ineffective and higher concentrations produced an opposite effect, ie, inhibited the release of serotonin; whereas in patients, lower concentrations of cisplatin induced less vomiting and less serotonin release than high concentrations of the agent).

Limitations of the 5-Hydroxy-indoleacetic Acid Measurements

Measurements of 5-HIAA are performed in the absence of better biochemical estimators of intestinal serotonin release in humans. Although 5-HIAA is the main metabolite of serotonin in humans, other metabolites also may be increased. Clearly, 5-HIAA is not a direct index of the concentration of serotonin at the 5-HT_3 receptors involved in the emetic response to chemotherapy. This may help explain the lack of relationship reported between the magnitude of the increases in 5-HIAA and the severity of the emetic response.[10]

There is a substantial intersubject (coefficient of variation = 33%) and intrasubject (coefficient of variation = 14%) variation in the daily urinary excretion of 5-HIAA in healthy individuals. Part of this variability could be due to dietary factors. For example, dietary protein (tryptophan) restrictions decrease by nearly half the urinary excretion of 5-HIAA in healthy volunteers.[42] Furthermore, avoidance of substances of a high serotonin content (eg, bananas, nuts, avocado) is recommended for accurate determinations of urinary 5-HIAA. In addition, cancer patients often are malnourished and do not ingest a normally balanced diet. These patients may have abnormal intakes of tryptophan and serotonin, which may alter the excretion of 5-HIAA. These dietary factors may produce substantial noise in the interpretation of the 5-HIAA data; consequently, urinary 5-HIAA may not be sensitive enough to detect small changes in the release and/or turnover of gastrointestinal serotonin. The noise of the 5-HIAA levels is reduced when each subject is used as his or her own control (at least two baseline measurements) and when measurements of the rate of excretion are used. Therefore, in our studies, repeated longitudinal measurements of the excretion of 5-HIAA at 2-hour intervals for periods up to 12 to 16 hours were taken. With this approach the changes are magnified and the time course for the changes can be estimated. In fact, if 24-hour measurements were to be used, the increases in 5-HIAA produced by high-dose cisplatin would be only 50% above previous-day excretion and may not even surpass what are considered the accepted high–normal values for the daily excretion of 5-HIAA. However, threefold increases above baseline can be observed if serial 2-hour measurements are performed.

OTHER SEROTONIN RECEPTORS INVOLVED IN VOMITING

The role of serotonin in nausea and vomiting is not limited to agents such as irradiation and cytotoxics. Recently, it has been demonstrated that 8-hydroxy-2-(di-n-propylamine) tetralin and buspirone, drugs that activate 5-HT_{1A} receptors, suppress vomiting induced by motion sickness, xylazine (an alpha-2 agonist), and cisplatin in laboratory animals.[43,44] However, the selective antagonists of 5-HT_3 receptors block emesis evoked by cisplatin but failed to affect vomiting induced by motion sickness or xylazine.[45] Recent studies revealed that the serotonin agonist RU 24969 produces emesis in the cat,[46] possibly through an action on 5-HT_{1D} receptors. 8-Hydroxy-2-(di-n-propylamine) tetralin also blocked emesis induced by RU 24959, suggesting that this compound has a general antiemetic effect in cats.

The participation of 5-HT_4 receptors in the emetic response to copper sulfate and to zacopride has been recently proposed.[47] Dumuis et al[48] demonstrated that at high concentrations, ICS 205930 acts as an antagonist of the putative 5-HT_4 receptors. This agent, in high concentrations, prevented zacopride-induced emesis as well as the emesis evoked by intragastric administration of copper sulfate, whereas selective 5-HT_3 receptor antagonists failed to do so.[47] Copper sulfate is thought to induce emesis when present in the gut lumen by activation of gastrointestinal mucosal chemoreceptors with afferents in the vagus.[47] Activation of these receptors may lead to the release of gastrointestinal serotonin, which may activate 5-HT_4 receptors located in vagal afferents.

These results suggest that several subtypes of serotonin receptors appear to be involved in the peripheral and central organization of the vomiting reflex. In addition, vomiting may be elicited by a variety of agents whose common effect is to induce the release of serotonin. Activation of 5-HT_{1A} receptors by drugs such as buspirone and 8-hydroxy-2-(di-n-propylamine) tetralin suppress emesis, whereas activation of 5-HT_3, 5-HT_{1D}, and 5-HT_4 receptors may induce emesis. In laboratory animals, the antiemetic effect produced by

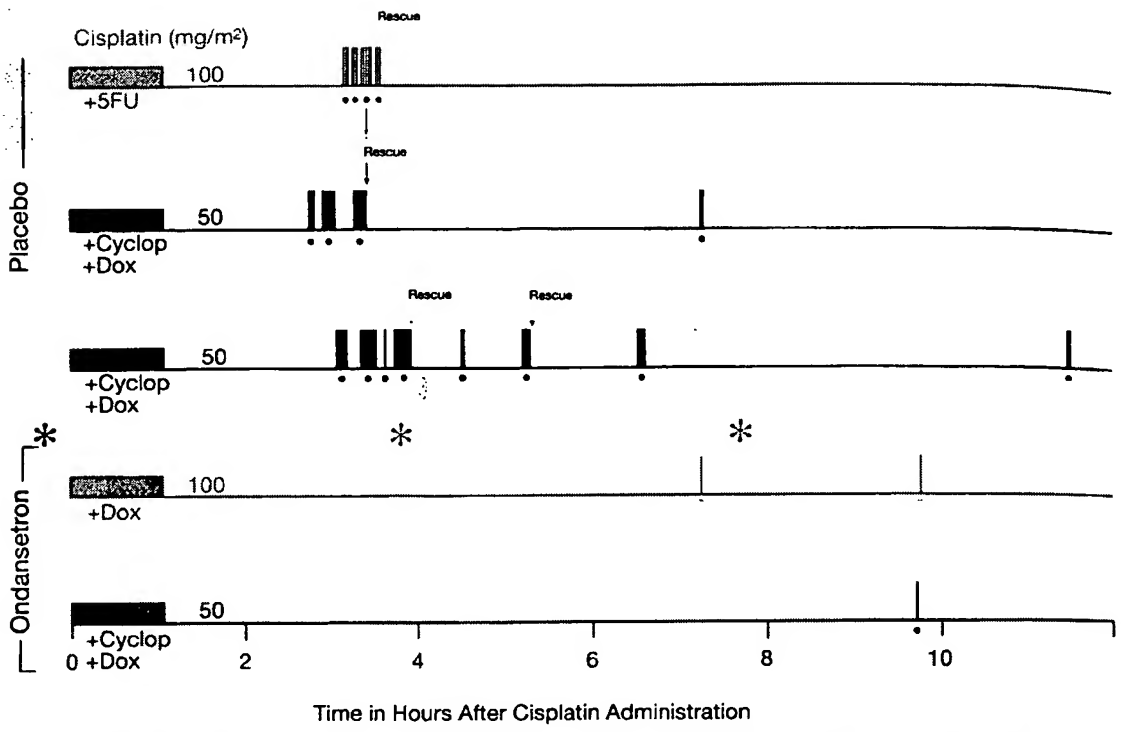

Fig 1. Effects of ondansetron on cisplatin-induced emesis in cancer patients. Shown are the emetic episodes (sets of vertical lines) induced by cisplatin in five patients. The first three patients received no antiemetic protection; the last two patients received ondansetron (0.15 mg/kg intravenously every 4 hours × 3). The intensity of the emetic episodes is directly related to the number of vomits per episode (number of vertical lines). Each vertical line indicates one vomit. Rescue antiemetic as previously described[10] was used (once or twice if needed) to stop emesis. Ondansetron blocked the early, intense period of emesis. Only late and very mild emetic episodes were observed after ondansetron (delayed emesis?). * Time of ondansetron administration.

5-HT_{1A} agonists is unspecific, protecting against a wide range of emetic stimuli, whereas the emetic effect mediated by 5-HT_3 receptor stimulation appears to be selective for chemotherapy and radiation therapy. The site at which serotonin is released by each of the emetic stimuli could determine the type of receptor activated as well as the efficacy of the antagonists. If serotonin is released in the vicinity of vagal afferent fibers and/or in the CTZ, where high concentrations of 5-HT_3 receptors are found, then drugs such as ondansetron and granisetron would provide antiemetic protection. In addition, if the 5-HT_{1A} receptors are located on the vomiting center or at sites that modulate the sensitivity of the vomiting center, activation of these receptors prevents vomiting evoked by most emetic stimuli. Clinical studies on the efficacy and safety of the 5-HT_{1A} agonists and of 5-HT_4 antagonists are required to establish their potential clinical use as antiemetics. These agents could be given either alone or with 5-HT_3 antagonists to ensure complete antiemetic protection of all patients receiving chemotherapy. Time and effort will provide the answer.

EFFICACY OF ONDANSETRON IN THE MANAGEMENT OF CHEMOTHERAPY-INDUCED EMESIS: ITS RELATIONSHIP WITH SEROTONIN-DEPENDENT AND -INDEPENDENT MECHANISMS

The efficacy data for selective 5-HT_3 antagonists reveal that these agents are very effective against chemotherapy-induced nausea and emesis; nevertheless, a significant proportion of patients still present some degree of nausea and emesis. For example, 7% to 30% of patients receiving cisplatin present five or more emetic episodes despite treatment with intravenous on-

dansetron.[10,49] Unfortunately, the multicenter nature of most studies precludes the gathering of information about the intensity of the emetic episodes. In these studies, an emetic episode could consist of either a single retch or five retches and six vomits; however, each will count as an emetic episode (Fig 1). When cisplatin-treated patients receive poor antiemetic coverage, the emetic episodes are very intense, consisting of several retches followed by several vomits (Fig 1). When the patients receive ondansetron the emetic episodes, when present, are very mild; in fact, of the patients who vomit, 73% have emetic episodes consisting of a single vomit with no or minimal retching. In summary, the patients who vomit despite treatment with ondansetron (0.15 mg/kg every 4 hours × 3) experience emetic episodes of very low intensity (Fig 1). Unfortunately, in most trials each episode is counted as one, regardless of its intensity. Another aspect that deserves attention is the time to the onset of emesis (latency time). It has been shown that 5-HT_3 antagonists produced a marked prolongation of the latency time. For example, for cisplatin-based chemotherapies the median time to onset of emesis was 2.8 hours in the placebo group and 11.6 hours in the ondansetron-treated group (Fig 1).[10] In another study with a larger number of patients, the mean latency time varied from 19 to 23 hours, depending on the dose of ondansetron.[49]

The findings described above suggest that ondansetron is more effective than the numbers indicate if drug efficacy is assessed by means of response rates (complete, major, minor, and failures), which is based on the number of emetic episodes. In fact, the residual mild emesis (occurring despite high-dose ondansetron) may never be fully prevented with selective 5-HT_3–receptor antagonists. It may well be that this emesis is mediated by mechanisms different (serotonin-5-HT_3–independent emesis) from those that mediate the early, intense period of emesis (serotonin-5-HT_3–dependent emesis). The latter is fully blocked by ondansetron. The residual emesis may be what is known as "delayed emesis," which for practical purposes has been defined as emesis that develops 24 hours after cisplatin. This definition is only operational, since both the cause and the time at which delayed emesis develops are unknown. Consequently, it is proposed that most of the episodes of emesis that develop after high-dose ondansetron (residual emesis) should be considered as delayed emesis. This is supported by the following data: (1) residual and delayed episodes of emesis have similar time courses, (2) both types of emesis are characterized by infrequent and very mild emetic episodes,[10] (3) delayed emesis is poorly responsive to ondansetron (as is residual emesis),[50] and (4) the urinary excretion of 5-HIAA is increased during the first 24 hours, but not at the times at which delayed and residual emesis develop.[31] The results suggest that most episodes of emesis developing after high-dose ondansetron (termed "residual" or "delayed") are mediated by serotonin-5-HT_3–independent mechanisms.

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